UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,629	09/21/2001	Peter Knox	PA-9848	5709

36335 7590 10/04/2006

GE HEALTHCARE, INC.
IP DEPARTMENT
101 CARNEGIE CENTER
PRINCETON, NJ 08540-6231

EXAMINER	
LAM, ANN Y	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,629	KNOX ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-15,20,24-27,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-15,20,24-27,30 and 31* is/are rejected.

7)☒ Claim(s) *1,8-10,12,15,20 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 2, 7, 16-19, 21-23, 28 and 29 are cancelled.

Claims 1, 3-6, 8-15, 20, 24-27, 30 and 31 are pending.

Specification

The disclosure is objected to because of the following informalities: there is no brief description of the drawings.

Appropriate correction is required.

Claim Objections

Claim 1 is objected to because of the following informalities: "hyperpolarising" and "hyperpolarisation" in step (b) should be changed to –hyperpolarizing—and –hyperpolarization--, respectively. Appropriate correction is required.

Claim 1 is objected to because of the following informalities: "analyzing" in step (c) should be –analyzing--. Appropriate correction is required.

Claim 8 is objected to because of the following informalities: "analysed" in step (c) should be –analyzed--. Appropriate correction is required.

Claim 9 is objected to because of the following informalities: "Nucleotide" should be –nucleotide--. Appropriate correction is required.

Claim 10 is objected to because of the following informalities: "hybridisation" should be --hybridization--. Appropriate correction is required.

Claim 12 is objected to because of the following informalities: --and wherein— should be inserted after the comma in line 3 (otherwise the claim is grammatically confusing.)

Claim 15 is objected to because of the following informalities: "hyperpolarisation" in line 3 should be –hyperpolarization".

Claim 20 is objected to because of the following informalities: "hyperpolarisation" and "polarisation" in step claim 20 should be changed to –hyperpolarization—and –polarization--, respectively. Appropriate correction is required.

Claim 31 is objected to because of the following informalities: one of the recitation of "the assay reagent" in lines 1-2 should deleted as being redundant. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 27 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "high" in claims 4 and 5 respectively is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 27, lines 2-3, recites the limitations "the well, surface or container". The claim lacks antecedent basis for these limitations. It is not clear whether or not "the well, surface or container" is referring to these limitations in the aerosol or flow-through device.

As to claim 30, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 5 recites the broad recitation "wherein the assay reagent contains an artificially high concentration of the NMR active nucleus in up to 10 defined positions", and claim 30,

which depends from claim 5, also recites "wherein the assay reagent contains an artificially-enriched abundance of the NMR active nucleus in one specific position", which is the narrower statement of the range/limitation. Thus, claim 30 is vague and indefinite as to how many positions are being referred to in claim 30. It is noted that while claim 5 uses the term "artificially high concentration" and claim 30 uses the term "artificially-enriched abundance", the term "artificially high concentration, because of its vagueness as to its meaning (see above), is interpreted to mean "artificially-enriched abundance" (which appears to be Applicant's intention, as shown by the present amendment to claim 30.) Also, it is noted that while claim 5 uses the term "defined" and claim 30 uses the term "specific", the terms are equivalent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-6, 8-9, 11-15, 20, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH_2-terminal

DNA-binding domain of *lac* respressor with poly[d(AT)]", Biochemistry, Vol. 77, No. 9, pp.5145-5148.

Yu discloses performing an assay on a biological species using an assay reagent (col. 40, lines 37-38) containing at least one NMR active nucleus (col. 40, lines 40-45) to perform an assay, said assay reagent being introduced as an initial reagent, formed in situ during the assay or formed as a product of the assay (col. 8, lines 56-59);

and analyzing the assay reagent and/or the assay by NMR for a physical or chemical change in the biological species that is independent of the interaction of the biological species with the NMR active nucleus, ^{13}C or ^{15}N (i.e., binding between receptor and agent, column 9, lines 8-19; column 40, lines 37-45, and column 41, lines 41-48.)

Examiner notes that the step of "optionally using the NMR data obtained to generate further assay results" in subsection (d) of claim 1 is only an option and thus is not a required limitation in the claims.

Although Yu teaches use of NMR spectroscopy in conjunction with an NMR active nucleus to analyze an assay, Yu does not teach hyperpolarization of the NMR active nucleus. However, Buck et al. this limitation.

Buck et al. teach that the disclosed photo-chemically induced dynamic nuclear polarization increases the NMR signal intensities of a binding assay method (see page 5145, see abstract and see right column, first full paragraph). (The section on materials and methods used, on page 5145, disclosed by Buck et al. shows that the reagents are

in solution form and thus, the assay is considered to be a liquid state assay method, as claimed by Applicant).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize dynamic nuclear polarization as taught by Buck et al. in the assay taught by Yu because Buck et al. teach that the dynamic nuclear polarization provides the benefit of enhancement in NMR signal intensities, such as the NMR signals in the Yu method.

Also, neither Yu nor Buck et al. teach that the degree of hyperpolarization of the NMR active nucleus is in excess of 0.1%. However, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art (In re Aller, 105 USPQ 233). In this case, Yu in view of Buck et al. teach the general conditions of the claim and the degree of hyperpolarization being in excess of 0.1% is within a workable or optimum range and thus its discovery involves only routine skill in the art.

As to the following claims, Yu teaches the limitations as follows.

As to claim 3, the NMR active nucleus is ^{13}C or ^{15}N (col. 40, line 45).

As to claims 4 and 5, the assay reagent is a compound which contains an artificially high concentration of an NMR active nucleus, (i.e., the NMR active nucleus added as a label to a reagent is considered to be artificially high concentration; col. 8, lines 57-58, and col. 40, lines 40-45.) As to claim 5, since the limitation "in 1-10 defined positions" is vague and indefinite (see above), the concentration of the NMR active nucleus in the Yu disclosure is considered to be in the 1-10 defined positions.

As to claim 6, the assay reagent is an organic compound comprising one or more NMR active nuclei associated with a bond which is broken during the course of the assay (i.e., the competitive displacement assay in col. 55, lines 54-56.)

As to claim 8, the analyzing step is repeated to generate information about a change with time of the assay reagent (i.e., a before and after detection.)

As to claim 9, the assay reagent is a polypeptide or protein (col. 8 lines 45-59.)

As to claim 11, the assay is a binding assay, (column 8, lines 45-59, or column 9, lines 8-19.)

As to claim 12, the assay reagent is a compound labeled with at least one NMR active nucleus (col. 40, lines 37-45), and the assay reagent is administered to micro-organism or cultured cells and cellular metabolites or an excretion product of the assay reagent are analyzed (see column 38, lines 9-15, disclose that the receptor can be utilized I a prokaryotic cell and the host cell expressing the receptor can be used whole and wherein the receptor can be free in the cytosol of the host cell).

As to claim 13, the assay is a binding study using micro-organisms or cultured cells, (column 38, lines 9-12.)

As to claim 27, Yu also teaches that the analyzing step is performed in an aerosol or flow-through device applied to aerosol droplets where the container is used to contain the assay reagent (col. 42, lines 11-20).

As to claim 14, while Buck et al. do not explicitly state that the hyperpolarization is repeated to enhance the signal-to-noise ratio, the hyperpolarization assay taught by Buck et al. is detected over time and thus hyperpolarization is performed over a period

of time. Thus the hyperpolarization is repeated and the assay results show the signal as well as noise, and thus the repeating of the hyperpolarization enhances the signal-to-noise ratio. See also page 5146, wherein the description of figure 3 states that 20 scans were accumulated.

As to claim 15, while Buck et al. do not teach that the shortening effect as expressed by the improvement of signal-to-noise per unit time is a factor of 10 or more compared to said method being carried out without hyperpolarization (as recited in claim 15). However, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art (In re Aller, 105 USPQ 233). Yu in view of Buck et al. teach the general conditions of the claim, and thus the discovery of the improvement of signal-to-noise by a factor of 10 or more compared to the method carried out without hyperpolarization requires only ordinary skill in the art.

As to claim 20, Buck et al. do not teach that the hyperpolarization transfer is carried out at a temperature of 4.2 K or less in the presence of a magnetic field of at least 1T. However, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art (In re Aller, 105 USPQ 233), and in this case, the temperature as claimed by Applicant is an optimum or workable range.

As to claim 30, the assay reagent is considered to contain an artificially-enriched abundance of the NMR active nucleus

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH_2-terminal DNA-binding domain of *lac* respressor with poly[d(AT)], and further in view of Katahira et al., "NMR studies of G:A mismatches in oligodeoxyribonucleotide duplexes modeled after ribozymes", Nucleic Acids Research, 1993, Vol.21, No. 23, pp. 5418-5424.

Yu in view of Buck et al. teach the invention substantially as claimed (see above with respect to claim 1). More specifically, as to claim 10, Yu et al. teach that the assay using NMR technique is a nucleic acid hybridization assay (see column 8, lines 60-67.) Moreover, while Buck et al. teach that photochemically induced dynamic nuclear polarization (i.e., photo-CIDNP) increases the NMR signal intensities of an assay method (see page 5145, see abstract and see right column, first full paragraph), Buck et al. do not teach that the assay is a hybridization assay. Rather Buck et al. teach that the assay relates to the binding between a protein and an oligonucleotide (see abstract on page 5145). Buck et al. is silent as to whether dynamic nuclear polarization can be utilized in a hybridization assay. However, Katahira et al. teach this limitation.

Katahira et al. teach that photochemically induced dynamic nuclear polarization (i.e., photo-CIDNP) in an NMR method can be used to study base pairing, i.e., hybridization (see page 5422, left column, third full paragraph, disclosing that the testing was done in solution form). It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize photochemically induced dynamic nuclear polarization as taught by Katahira et al. to study a hybridization assay, such as the

hybridization assay disclosed by Yu. One of ordinary skill in the art would have reasonable expectation of success because Buck et al. teach that photochemically induced dynamic nuclear polarization provides the benefit of enhancing NMR signals in an assay method, and Katahira et al. specifically teaches that the NMR detection using dynamic nuclear polarization can be used to detect base pairing, i.e., hybridization, such as the hybridization assay disclosed by Yu.

Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH_2-terminal DNA-binding domain of *lac* respressor with poly[d(AT)]", Biochemistry, Vol. 77, No. 9, pp.5145-5148, as applied to claim 1, and further in view of Obremski, 6,110,749.

Yu in view of Buck et al disclose the invention substantially as claimed (see above with respect to claim 1), except for more than one assay being multiplexed (claim 24), and for the assay being performed in a multispot assay array (claim 25).

However Obremski teaches channels which confine liquid samples and confine light to desired areas and that this is useful in the simultaneous assay of multiple samples, as well as multiple target analytes (col. 7, lines 5-8). This configuration is deemed to be a multiplexed or multispot assay as claimed by Applicant. It would have been obvious to one of ordinary skill in the art to provide a multiplexed or multispot assay as taught by Obremski using the Yu in view of Buck et al. method of analysis,

because Obremski teach that it is useful for simultaneous assay of multiple samples as well as multiple target analytes, as would be desirable for convenience.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH_2-terminal DNA-binding domain of *lac* respressor with poly[d(AT)]", Biochemistry, Vol. 77, No. 9, pp.5145-5148, as applied to claim 1, and further in view of Pines et al., 6,426,058

Also, as to claim 26, Yu in view of Buck et al. teach the invention substantially as claimed (see above), except for the analyzing step being performed by using both NMR spectroscopy and magnetic resonance imaging, and repeating the examination at least once.

Pines does however teach that a sample can be analyzed using both NMR spectroscopy and magnetic resonance imaging (see column 8, lines 60-63), and that multiple parameters can be detected, and multiple techniques can be employed to collect and manipulate nuclear magnetic resonance data (col. 19, lines 3-5.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize MRI detection as taught by Pines in the method taught by Yu in view of Buck et al. because Pines teaches that NMR spectroscopy and MRI detection can both be used to analyze a sample, as would be desirable for the analysis of the assay.

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of , in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH_2-terminal DNA-binding domain of *lac* respressor with poly[d(AT)]", Biochemistry, Vol. 77, No. 9, pp.5145-5148, as applied to claim 1, and further in view of Neild et al., "Uroscopy in the 21st Century: high-filed NMR spectroscopy", Nephrol Dial Transplant (1997), 12: 404-417.

Yu in view of Buck et al. teach the invention substantially as claimed (see above), except for the assay reagent being an organic compound comprising two or more NMR active nuclei associated with a chemical bond which is broken during the course of the assay such that when the bond is intact, the NMR active nuclei are spin coupled and when the bond is broken the spin coupling is disrupted. Neild et al. teach this limitation however.

Neild et al. teach that individual magnetic nuclei can interact with each other to produce additional splittings of the NMR peaks, called spin-spin or J coupling (see page 405, left column). Neild et al. teach that these interactions are also used for structural identification since they depend on molecular shapes and conformations (page 405, left column.) It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the spin coupling as taught by Neild et al. in the Yu invention because Neild teaches that such spin coupling provides the advantage of structural identification.

Response to Arguments

Applicant's arguments filed September 18, 2006 has been considered but are not persuasive. Applicant states that the degree of hyperpolarization of the NMR active nucleus covered by the presently claimed invention is in excess of 0.1%. Applicant asserts that none of the references teach this limitation. Applicant points out that figure 3 of Buck et al. illustrates the best enhancement, in particular the peak present at just over 7 ppm. Applicant states that to calculate the degree of polarization, the thermal equilibrium is multiplied by the level of enhancement. Applicant asserts that the maximum enhancement achieved using photo-CIDNP according to Buck et al. is 20, resulting in a degree of polarization of 0.056%, which is clearly below the minimum required by the presently claimed invention. This argument is not persuasive because Buck et al. (in addition to Yu) teach the general conditions of the claim. Specifically, Buck et al. teach hyperpolarization to enhance NMR technique because it increases the NMR signal intensities of a binding assay method (see page 5145, see abstract and see right column, first full paragraph). The assay performed by Buck et al. is only an example of a hyperpolarization assay rather than being a limitation on the hyperpolarization technique disclosed by Buck et al. It is also noted that there is no showing by Applicant that Applicant's hyperpolarization technique is any different from that disclosed by Buck et al. The degree of hyperpolarization being in excess of 0.1% is a workable or optimum range, and thus its discovery would involve on routine skill in the art under *In re Aller*, as discussed above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

9/28/06

Ann Lam